Collaborative overview of randomised trials of antiplatelet therapy—II: Maintenance of vascular graft or arterial patency by antiplatelet therapy

Antiplatelet Trialists' Collaboration

Part I of this overview, on preventing vascular events with prolonged antiplatelet therapy, was published last week. The concluding part, on preventing venous thromboembolism, will be published next week.

Abstract

***Objective*—To determine the efficacy of antiplatelet therapy in maintaining vascular patency in various categories of patients.**

***Design*—Overviews of 46 randomised trials of antiplatelet therapy versus control and 14 randomised trials comparing one antiplatelet regimen with another.**

***Setting*—Randomised trials that could have been available by March 1990 and in which vascular graft or arterial patency was to be studied systematically.**

***Subjects*—About 8000 patients at varying degrees of risk of vascular occlusion (by virtue of disease or of having some vascular procedure) were in trials of antiplatelet therapy versus control and 4000 such patients were in trials directly comparing different antiplatelet regimens.**

***Results*—Overall, antiplatelet therapy produced a highly significant ($2P < 0{\cdot}00001$) reduction in vascular occlusion, with similar proportional reductions in several different types of patient. Hence the absolute reductions tended to be largest among patients at highest risk of occlusion, with smaller but still significant absolute reductions among lower risk patients. The proportions of patients with confirmed occlusion among those allocated antiplatelet therapy versus appropriately adjusted control proportions (and mean scheduled treatment durations and net absolute benefits) were: (*a*) among about 4000 patients with coronary artery grafts, 21% antiplatelet therapy *v* 30% control (seven month benefit about 90 patients protected per 1000 allocated antiplatelet therapy ($2P < 0{\cdot}00001$)); (*b*) among about 800 patients after coronary angioplasty, 4% antiplatelet therapy *v* 8% control (six month benefit about 40/1000 ($2P = 0{\cdot}02$)); (*c*) among about 3000 patients with peripheral artery procedures or disease, 16% antiplatelet therapy *v* 25% control (19 month benefit about 90/1000 ($2P < 0{\cdot}00001$)); (*d*) among about 400 renal patients with a shunt or fistula placed for haemodialysis access, 17% antiplatelet therapy *v* 39% control (two month benefit about 200/1000 ($2P < 0{\cdot}00001$)).**

Indirect comparisons between the effects of starting treatment before these vascular procedures and starting soon after them indicated similar sized benefits. As well as preventing subclinical occlusion, antiplatelet therapy produced a significant ($2P = 0{\cdot}002$) reduction of about one quarter in the odds of suffering a "vascular event" (non-fatal myocardial infarction, non-fatal stroke, or vascular death). Various antiplatelet regimens (chiefly aspirin alone or aspirin plus dipyridamole) were studied but there was no significant evidence of differences between their effects on arterial occlusion or vascular events. Data on bleeding were incomplete but no large excess with antiplatelet therapy was apparent.

***Conclusion*—Antiplatelet therapy (chiefly aspirin alone or aspirin plus dipyridamole) greatly reduces the risk of vascular occlusion in a wide range of patients at high risk of this complication. Further studies are required to determine exactly when treatment should start (to limit any perioperative bleeding while still preventing most early occlusion) and for how long it should be continued.**

Antiplatelet Trialists' Collaboration
A full list of collaborators was given at the end of part I.

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Introduction

After coronary artery revascularisation, whether by coronary artery bypass grafting or by percutaneous transluminal coronary angioplasty,[1] angiographic studies show substantial rates of reocclusion. For example, about one fifth of coronary artery bypass grafts occlude during the first postoperative year[2] and a few per cent per year occlude thereafter.[3,4] These occlusions are often subclinical, though some may produce clinical signs of myocardial infarction.[5] Occlusion or reocclusion is also seen after peripheral artery revascularisation, though many such occlusions also are subclinical. Finally in patients with renal disease who have arteriovenous fistulas or shunts established to allow haemodialysis, occlusion of these is common (and such patients are also at particularly high risk of other serious thrombotic complications[6]). Experimental[7,8] and clinical[5,9-11] evidence suggests that antiplatelet therapy may help prevent vascular graft or arterial occlusions, particularly during the period soon after vascular procedures, before any intimal damage has healed.

Randomised evidence of the effects of antiplatelet therapy on myocardial infarction, stroke, and death was reviewed in part I.[5] To assess the effects of this treatment on vascular occlusion this paper provides a systematic overview[12,13] of all randomised trials of antiplatelet therapy in which vascular graft or arterial patency was to be studied systematically. (This includes arteriovenous shunts but excludes those trials in which the chief aim was to prevent deep venous thrombosis or pulmonary embolism, which are reviewed separately in part III.[9]) Wherever possible information on any serious bleeding complications was also reviewed.

Materials and methods

DATA ACQUISITION

Identification of all unconfounded randomised trials

The aim was to include all unconfounded randomised trials of antiplatelet therapy versus no antiplatelet therapy, or of one antiplatelet regimen versus another, that could have been available for review by March 1990 and in which vascular graft or arterial patency was monitored systematically (see appendices 1 and 2). A fuller description of the methods used for seeking trials

and data was given in part I.[5] Relevant randomised trials were identified in three main categories: (*a*) coronary artery trials—patients having coronary artery bypass grafting[14-43] or percutaneous transluminal coronary angioplasty[44-46]; (*b*) peripheral artery trials—patients with symptomatic peripheral vascular disease in whom patency of native peripheral arteries[47-50] was studied, patients having any non-coronary arterial grafting procedures (usually in the legs),[51-65] or patients having transluminal angioplasty in the legs[66-69]; (*c*) haemodialysis access trials—patients with arteriovenous fistulas or shunts placed for haemodialysis.[70-82]

As in part I, trials were to be excluded if allocation was believed not to have been randomised in a manner that precluded prior knowledge of the next treatment (for example, where allocation was alternate or based on odd or even dates, or where the comparison was to be with some historical controls) or if the treatment comparisons were considered to be confounded (that is, where the scheduled treatment in one group differed from that in the other in some aspect other than antiplatelet therapy). Nor were randomised trials to be included that did not seek vascular graft or arterial occlusion systematically (for example, those designed to assess only partial vessel occlusion, only clinical events, or only short term haematological changes (see appendices 1 and 2 in part I)). Trials that were not available for review by March 1990, generally because they were still in progress (see references in part I), do not contribute to the main analyses, though the larger such trials that were reported subsequently are included in appendices 1 and 2 and the discussion.

Definition of outcome measures

Methods used to assess vascular patency varied widely between trials: angiography in all coronary artery trials; clinical examination, Doppler ultrasonography, limb plethysmography (often with confirmatory radionuclide scanning or angiography), or systematic angiography in peripheral artery trials; and clinical examination in all haemodialysis access trials (see appendices 1 and 2). But within any single trial the same approach was to be used for assessing both treatment and control patients, so variation between different trials in the methods used does not invalidate an appropriately constructed overview of their separate results. In some surgical settings, particularly in the coronary circulation, one patient might receive several grafts, but data were sought only on the number of patients in each treatment group who suffered at least one main proximal graft occlusion within the scheduled follow up period. Similarly, for renal patients, in whom multiple occlusions might occur sequentially in the same arteriovenous fistula or shunt, the information sought was whether any occlusions had occurred.

Many trials also attempted to assess "partial occlusion," but there are substantial difficulties with this. (For example, among patients who have had percutaneous transluminal coronary angioplasty the proportion suffering it varies from 2% to 20%,[83] depending on the definition used.) This report therefore excludes partial occlusions. The denominator was to be the number of patients originally randomised rather than the number who received follow up angiography or some other form of assessment of vascular patency. Inevitably, when the method of assessing arterial or graft occlusion was invasive some patients were not subjected to it (see appendices 1 and 2). In principle this might bias outcome assessment, particularly if treatment influenced the rate of symptomatic occlusion, but in practice within any one trial the proportions assessed were generally similar in the treatment and control groups. Analyses confined to placebo controlled studies, which may be less subject to treatment dependent biases in the assessment of vascular occlusion, were also considered separately when appropriate.

Information on non-fatal clinical events (such as myocardial infarction and stroke) and on death from vascular and other causes was also sought, though these events were often recorded only as secondary outcome measures. In the trials where treatment was to last at least one month such results already contribute to part I. Information was sought on any haemorrhage that was either fatal or severe enough to require transfusion (here defined as a "major" bleed), and was generally available. Other measures of perioperative haemorrhagic complications (such as bleeds resulting in reoperation, wound haematomas, or infection) were also sought, but the definitions used were not uniform and such measures were not available from most trials.

When the data collected did not include information about outcome among all patients initially randomly assigned on all of the outcomes of interest extra details were sought from the principal investigators (see part I). In trials in which some patients had been excluded after randomisation from the published report it was often possible to obtain by correspondence follow up information on these outcome measures among most or all of the missing patients, so that appropriately unbiased intention to treat analyses of such events could be conducted. When this was not possible the available data have still been included in the overview unless the number of exclusions was so extensive that the trial could no longer be considered properly randomised.

Statistical methods: proportional and absolute reductions

Statistical methods used to obtain an overview of the results from the trials were detailed in part I. Proportional reductions in vascular occlusion may be more widely generalisable to somewhat different medical settings, whereas absolute reductions may be more directly relevant to deciding whether to use therapy in particular medical settings. Standard methods for combining trial results[5 10 84 85] that provide an unbiased test of whether treatment has any effect at all can also provide an estimate of the "typical" proportional reduction in the odds of adverse events observed in the trials. (These methods are completely robust and assume not that the real proportional effects of treatment are all exactly the same in the different trials but merely that any real effects probably point in the same direction. Fuller discussion has been given elsewhere.[85]) When the overall difference between treatment and control patients is very highly significant and all the trials are approximately evenly randomised, a simple description of the absolute reduction can be provided just by adding together all the treatment groups, adding together all the control groups, and comparing these two grand totals. (If any of the trials involve deliberately uneven treatment allocation—for example, two thirds treatment versus one third control —then it can first be "adjusted" to an evenly randomised comparison by counting the control group more than once (see part I).)

Even when there is a highly significant overall effect, separate analyses of the effects in small subgroups of patients may be statistically unstable. Consequently, unless there are good prior reasons for expecting large differences between the effects of treatment in different circumstances, the approximate benefit of antiplatelet therapy in some particular subgroup may best be assessed indirectly, not from an analysis that is restricted just to that one subgroup but, instead, by approximate extrapolation from the proportional effect that is observed in a much wider class of patients[86] (see discussion in part I).

Results

EFFECTS OF ANTIPLATELET THERAPY ON VASCULAR GRAFT OR ARTERIAL OCCLUSION

Information on vascular graft or arterial occlusion was available from 46 trials of antiplatelet therapy. The proportional odds reductions are described in figure 1 and (of more direct relevance to medical practice) the absolute reductions in risk are given in figure 2. The numbers of patients suffering a vascular occlusion among those allocated antiplatelet therapy totalled 864/4889 (17·7%), while the corresponding adjusted total among controls was 1327/4911 (27·0%). These crude risks of 18% and 27% indicate a risk reduction of about one third, which corresponds to an odds reduction of somewhat more than one third (see legend to figure 1). More formal statistical methods for combining the results from these 46 trials, which entail no unjustified assumptions,[5] indicate that the typical reduction in the odds of a vascular occlusion occurring was about 44% (SD 4%), which is very highly significantly favourable ($2P < 0{\cdot}00001$; fig 1).

When the trials were subdivided into the three main patient categories (coronary artery, peripheral artery, and haemodialysis access trials) the odds reductions were highly significant in each separate category (each $2P < 0{\cdot}00001$; fig 1). The 46 separate trials did not all indicate exactly the same odds reduction, but the odds reductions in the two largest patient categories were similar to each other and only slightly smaller than that observed among dialysis patients. The consistency of the proportional effects observed in these very different clinical settings is important because it suggests a general finding of wide applicability. It is the absolute effects, however, that determine how worth while antiplatelet therapy is, and for these reasons both proportional (fig 1) and absolute (fig 2)

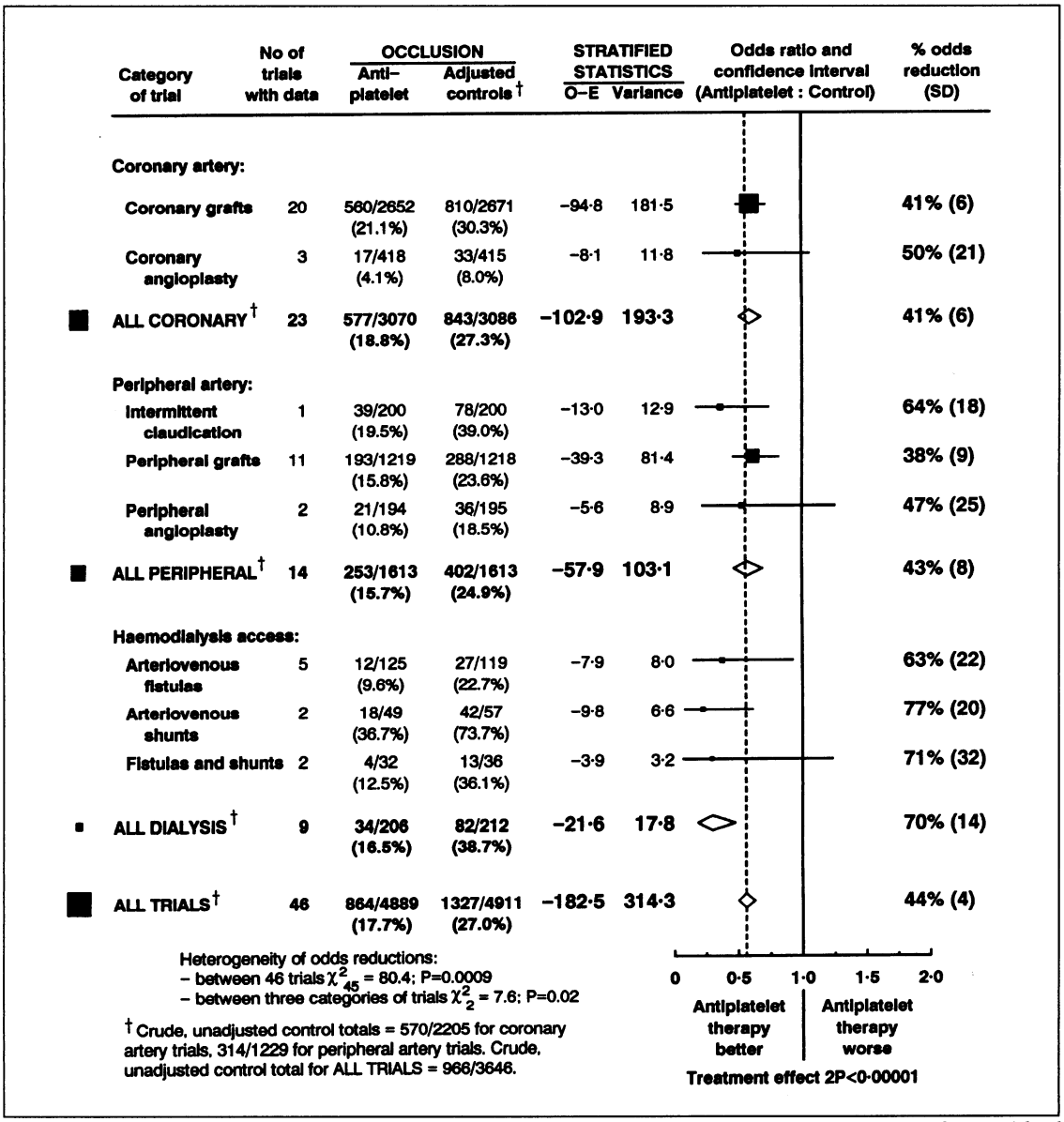

FIG 1—*Proportional effects of antiplatelet therapy on numbers of patients found to have occlusion after coronary artery procedures, peripheral artery procedures or disease, and after establishing haemodialysis shunts or fistulas. O–E = Observed minus expected.*

In most trials patients were allocated roughly evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparisons between proportions observed to have an event in each treatment group, adjusted totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once. Statistical calculations are, however, based on actual numbers from individual trials and crude, unadjusted control totals are given. Stratified ratio of odds of occlusion in treatment group to that in control group is plotted for each group of trials (black square: area proportional to amount of information contributed) along with its 99% confidence interval (horizontal line). Black square to left of solid vertical line suggests benefit (significant at $2P < 0{\cdot}01$ only where entire confidence interval is to left of solid vertical line). Overviews of results for certain subtotals of trials (and 95% confidence intervals) are represented by diamonds. Observed reductions in odds of occlusion in particular groups of trials are given to right of solid vertical line)

Risk reduction and odds reduction: Crude totals occluded (18% and 27%) suggest risk reduction of about one third but odds reduction of more than one third. These crude risks are equivalent to odds of 18/82 (0·22) and 27/73 (0·37) respectively (indicating odds ratio of about 0·22/0·37 (=0·59)—that is, approximate odds reduction of about 41%, which is similar to result (44% (SD 4%)) of more formal statistical analysis)

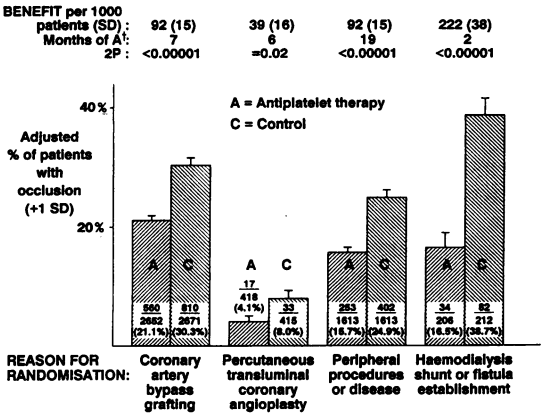

FIG 2—*Absolute effects of antiplatelet therapy on occlusion. Adjusted totals calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, for calculating adjusted percentages and numbers of patients prevented from having occlusion per 1000 allocated antiplatelet therapy. (Significance (2P) based on stratified analyses of original, unadjusted numbers in each trial: see statistical methods in part I). †Months of A = Means of scheduled antiplatelet durations*

reductions are described in the more detailed results that follow.

EFFECTS IN DIFFERENT CATEGORIES OF PATIENTS

Coronary artery trials

Thirty trials of antiplatelet therapy versus control were identified among patients who had had coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (see part I), but vascular occlusion was monitored systematically in only 23 of these trials. In these, allocation to antiplatelet therapy was associated with a proportional reduction of 41% (SD 6%) in vascular occlusion, which was highly significant ($2P < 0{\cdot}00001$; fig 1). Twenty of the 23 trials that could provide information on vascular occlusion concerned patients with coronary artery bypass graft surgery rather than angioplasty. The proportional reductions in the odds of suffering at least one occlusion appeared similar after coronary artery bypass grafting and after percutaneous transluminal coronary angioplasty. But although the reductions were significant in each setting ($2P < 0{\cdot}00001$ and $2P = 0{\cdot}02$ respectively), the former is much more accurately known. Among patients who had had coronary artery bypass grafting, allocation to a mean scheduled duration of seven months of antiplatelet therapy was associated with prevention of occlusion in 92 (SD 15) patients per 1000 (21·1% of antiplatelet allocated patients versus 30·3% of corresponding controls; fig 2). In the coronary angioplasty studies occlusion was less common (4·1% antiplatelet therapy *v* 8·0% control) but allocation to an average of six months of antiplatelet therapy nevertheless achieved an absolute reduction of 39 (SD 16) per 1000 patients.

Peripheral artery trials

Thirty nine trials of antiplatelet therapy versus control were identified among patients having peripheral vascular procedures or with peripheral vascular disease (see part I) but vascular occlusion was monitored systematically in only 14 of them. Allocation to antiplatelet therapy in these 14 trials was associated with a proportional reduction of 43% (SD 8%) in vascular occlusion, which was highly significant ($2P < 0{\cdot}00001$; fig 1). Studies of patients with saphenous vein grafts or prosthetic implants for lower limb disease contributed most of the data; of the three other studies, one assessed the patency of native vessels in patients with intermittent claudication and two concerned patients who had had peripheral angioplasty. As before, however, the proportional reductions in occlusion appeared similar in each of these three different settings, although only the first of the three is accurately known ($2P = 0{\cdot}00001$, $2P < 0{\cdot}0005$, and $2P = 0{\cdot}06$ respectively; fig 1). Overall, allocation to a mean scheduled duration of 19 months of antiplatelet therapy produced a substantial absolute reduction of 92 (SD 15) per 1000 in the risk of peripheral artery occlusion (15·7% of antiplatelet allocated patients versus 24·9% of corresponding controls; fig 2).

Haemodialysis access trials

Ten trials of antiplatelet therapy versus control were identified among renal patients having surgery to establish haemodialysis access, and vascular occlusion was monitored systematically in nine of these trials (all evenly balanced and placebo controlled) among a total of only 418 patients. Allocation to antiplatelet therapy in these nine trials was associated with a proportional reduction of 70% (SD 14%) in vascular occlusion, which was highly significant ($2P < 0{\cdot}00001$; fig 1). Similar sized proportional reductions in occlusion of fistulas and of shunts were observed, both being highly significant ($2P = 0{\cdot}005$ and $2P < 0{\cdot}0002$ respectively). Thrombotic occlusion of a fistula or shunt may occur rapidly, so that, although the mean duration of these trials was only two months, 38·7% of the controls suffered an occlusion as against only 16·5% of the antiplatelet allocated patients—an average absolute reduction of 222 (SD 38) per 1000 (fig 2). The risk of occlusion was greatest among patients in whom arteriovenous shunts were established, so that the absolute benefits observed with antiplatelet therapy among such patients appeared to be even greater than among those with fistulas.

Avoiding bias when assessing efficacy

Systematic assessment of patency was planned in all patients randomised in these trials, but the methods to be used differed widely (appendices 1 and 2). Variation of the method used to detect occlusion should not bias assessment of whether or not antiplatelet therapy prevents occlusion because within any particular trial the same technique was to be used for both the treatment and control groups. But as the methods used were sometimes rather subjective, ascertainment of occlusion might, in principle, have been influenced by knowledge of the allocated treatment group. In practice, however, the results (44% (SD 4%) proportional reduction overall, with 41% (SD 6%), 43% (8%), and 70% (14%) reductions in coronary artery, peripheral artery, and haemodialysis access studies respectively) were not materially altered when the analyses were confined to placebo controlled trials (43% (SD 4%) proportional reduction overall, and 40% (6%), 41% (8%), and 70% (14%) reductions in these three main categories).

As noted in part I, data dependent emphasis on analyses among specific categories of patients, or of trials, may lead to biased conclusions. Hence, though there was marginally significant heterogeneity (χ^2 on 2 df = 7·6; $P = 0{\cdot}02$) between the effects of antiplatelet therapy on vascular occlusion in the three different categories of patients, the effects in any particular category may best be assessed indirectly by approximate extrapolation from the 44% (SD 4%) reduction in occlusion observed in the overview of all trials rather than directly from the effects observed only in that one category (fig 1). Such arguments would not materially alter the size of the estimated effects on coronary or peripheral artery patency but would suggest that the effect among haemodialysis patients, though certainly real, may not be quite as large as these small trials indicate.

COMPARISONS OF DIFFERENT ANTIPLATELET REGIMENS

Indirect comparisons of when to start therapy

During the period covered by this overview there were no direct randomised comparisons of starting treatment before the invasive vascular procedure versus starting treatment after it. Indirect comparisons between the average effects observed in trials of treatment started before the procedure and the average

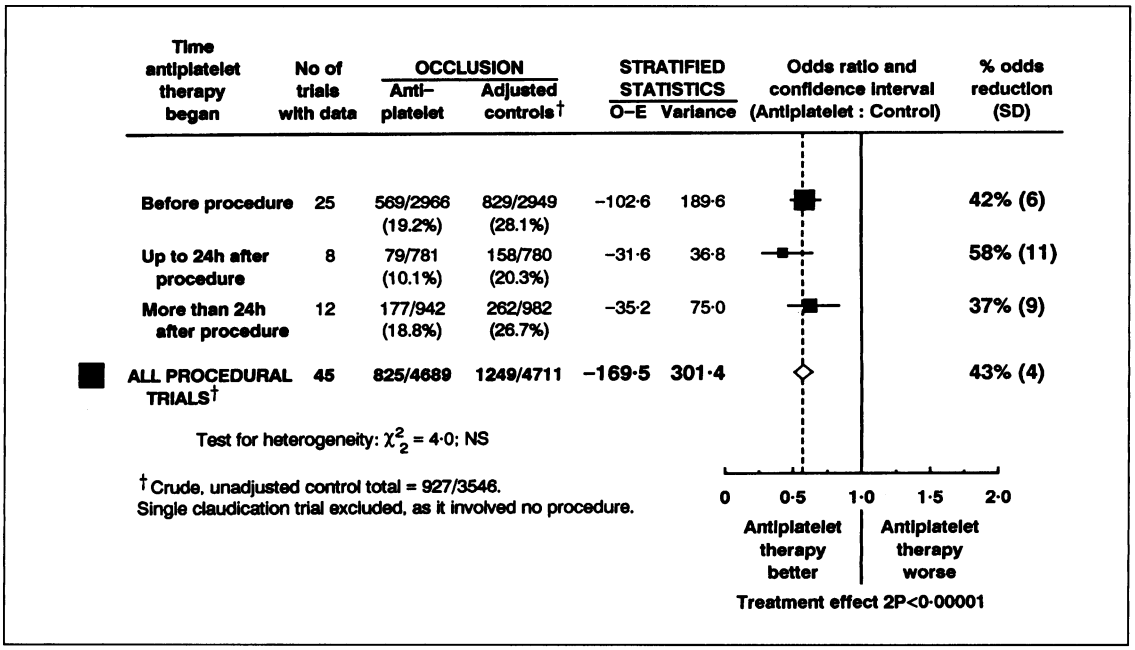

FIG 3—*Indirect comparisons of proportional effects of antiplatelet therapy started before or after vascular procedures on occlusion. Symbols and conventions as in figure 1*

effects in trials where it was started after the procedure indicated that similar reductions in vascular occlusion could be achieved by starting before the procedure or within the first 24 hours afterwards (fig 3). But even in trials of treatment started somewhat more than 24 hours postoperatively, a highly significant reduction in occlusion was observed that was not significantly different from that seen in the trials of treatment started earlier. Nevertheless, the right hand ends of the confidence intervals for the sizes of the effects in figure 3 (which indicate the minimum benefit that is readily compatible with the trial results) show that the size of benefit that is statistically guaranteed to exist by these trials is substantially greater if treatment is started reasonably promptly.

Direct and indirect comparisons of different regimens

The effects of different antiplatelet drug regimens (high dose aspirin, medium dose aspirin, aspirin plus dipyridamole, dipyridamole, sulphinpyrazone, ticlopidine, suloctidil) on "vascular events" (non-fatal myocardial infarction, non-fatal stroke, or vascular death) were reviewed in part I, with no clear evidence that one regimen differed much from another in its ability to prevent such vascular events. Likewise, in the present trials (figs 4, 5) of the prevention of vascular occlusion neither direct comparisons nor indirect comparisons of the effects of different regimens on vascular patency provided good evidence that any one antiplatelet drug regimen studied was more effective than any other.

Some direct randomised comparisons of the effects on occlusion were available (fig 4), but these were generally too small to be reliable. The only apparent trend was towards a slightly better effect with somewhat lower doses of aspirin, but that trend was not statistically significant (and parts I and III of this overview[59] suggest that higher and lower doses of aspirin are of about similar efficacy). Nevertheless, if aspirin is to be given to maintain arterial patency, then these trials provide no directly randomised evidence that higher (and hence more gastrotoxic[87 88]) aspirin doses are any more effective than 75-325 mg daily. Indirect comparisons of the effects observed on occlusion in separate overviews of trials comparing various different regimens with control (fig 5) likewise provide no clear evidence that any one antiplatelet regimen was more or less effective than another.

EFFECTS OF ANTIPLATELET THERAPY ON BLEEDING

The table summarises the bleeding complications reported in all trials comparing antiplatelet therapy with control in patients who were to undergo, or had just undergone, a vascular procedure, irrespective

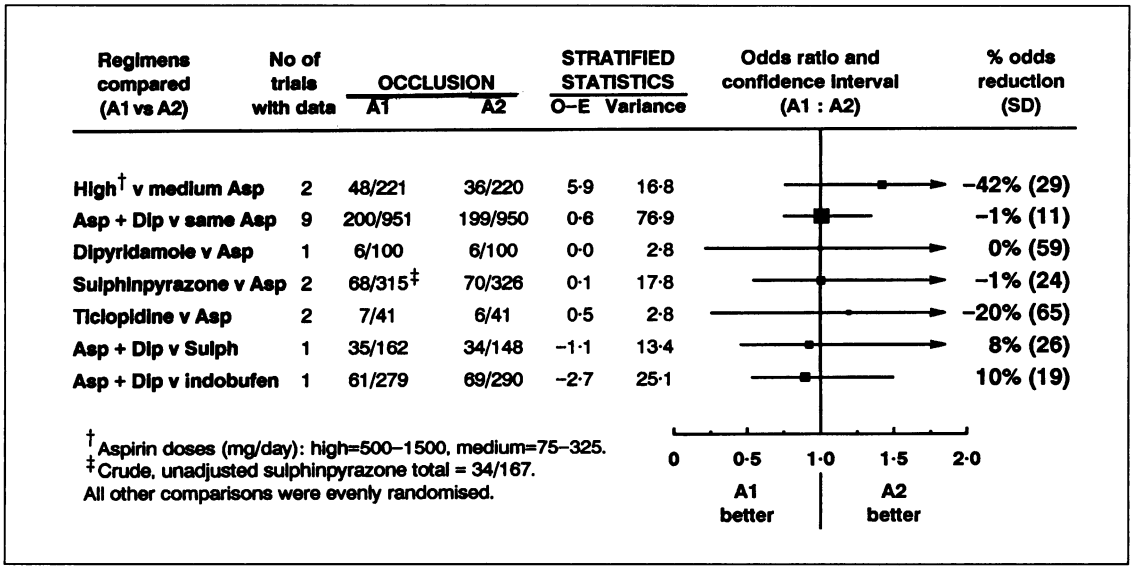

FIG 4—*Direct comparisons of proportional effects on occlusion of different antiplatelet regimens. Symbols and conventions as in figure 1. Asp=Aspirin. Dip=Dipyridamole. Sulph=Sulphinpyrazone*

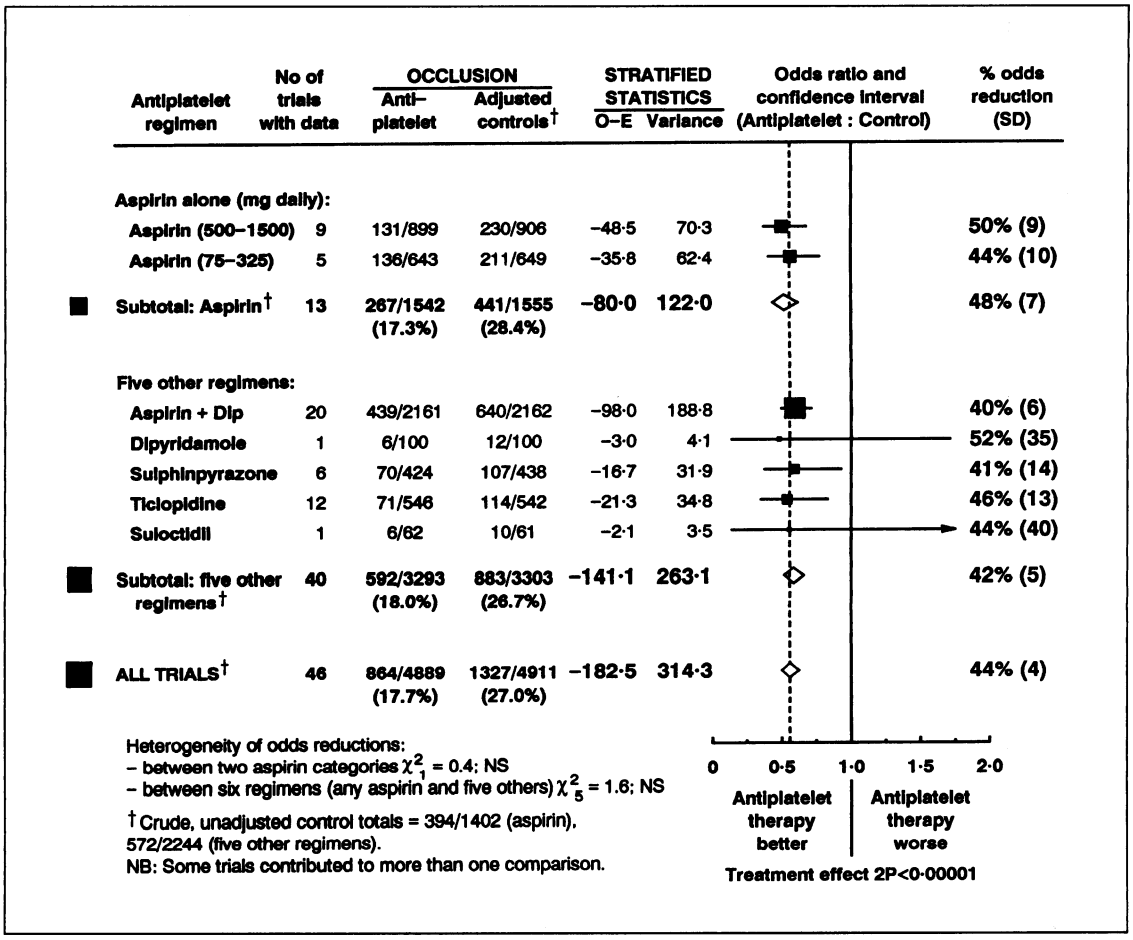

FIG 5—*Indirect comparisons of proportional effects on occlusion of different antiplatelet regimens. Symbols and conventions as in figure 1*

of whether vascular patency was to be monitored systematically.

Among the trials in which some months of antiplatelet therapy was to be started just before the procedure there was an apparent excess of about one fatal bleed per 1000 patients allocated antiplatelet therapy (95% confidence interval 0 to 3 per 1000), but it was not quite statistically significant. There was a significant excess of non-fatal "major" bleeds reported (2·2% *v* 0·9%; 1P=0·002) but the absolute excess was small (about 13 (SD 4) per 1000). Information on other complications (reoperations, wound haematomas, or infections due to bleeding) was available from only a few trials. No large excess was apparent, but the incompleteness of the data precluded reliable estimation of the exact size of any excess.

Among the trials in which some months of antiplatelet therapy was to be started after the vascular procedure, however—in many of which the treatment was to be started less than 24 hours afterwards—there was no apparent excess of fatal or non-fatal major bleeds (nine among patients allocated antiplatelet therapy versus an adjusted control total of five) or of other haemorrhagic side effects (one versus one).

Reported bleeding complications in all trials of antiplatelet therapy among patients having vascular procedures (irrespective of whether patency was monitored systematically)

Complication reported	Time antiplatelet therapy began	No of trials with data (No without)	Antiplatelet groups	Adjusted controls	Absolute excess per 1000 (SD)	Significance (1P)
Fatal bleed†	Before procedure	28 (3)	5/3267	1/3262	1 (1)	=0·06
	After procedure	19 (3)	1/1405	0/1450	1 (1)	NS
Non-fatal "major" bleed†	Before procedure	26 (5)	70/3214	29/3201	13 (4)	=0·002
	After procedure	18 (4)	8/1327	5/1367	2 (3)	NS
Reoperation, haematoma, or infection due to bleed‡	Before procedure	11 (20)	109/1997	72/2002	19 (7)	=0·02
	After procedure	4 (18)	1/418	1/430	0 (4)	NS

†"Fatal or non-fatal" bleeds were missing from one of 45 vascular procedure trials that provided data on occlusion and were available from five of eight vascular procedure trials that did not.
‡Data seriously incomplete, which may seriously distort results.

Discussion

SIMILAR PROPORTIONAL REDUCTIONS IN OCCLUSION IMPLY GREATER BENEFIT FOR THOSE AT HIGHER RISK

Among patients having coronary artery bypass operations, coronary artery angioplasty, leg artery bypass operations, or leg artery angioplasty, this overview of randomised trials provides unequivocal evidence that antiplatelet therapy (beginning either just before or, possibly slightly more safely, just after the procedure) reduces the odds of graft or arterial occlusion by about 40% while treatment continues. The numbers studied were largest, and hence the evidence was strongest, for patients having coronary and peripheral artery grafts, but there was also significant benefit after angioplasty. In absolute terms the benefits were substantial, occlusions being averted in about 40 to 90 patients per 1000 allocated antiplatelet therapy for about seven months after coronary artery procedures and about 19 months after peripheral artery procedures (fig 2).

When considering the effect of antiplatelet therapy it is important to remember that owing to non-compliance in the trials the trial results (and hence the present overview results) will systematically underestimate the size of the effect produced by actually taking treatment. Moreover, patients who have had vascular interventions are at high risk not just of subclinical occlusion but also of major vascular events such as myocardial infarction, stroke, or vascular death. Part I[5] showed that among many types of patients prolonged antiplatelet therapy prevents about a quarter of such vascular events, the effects being

about as great (22% (SD 7%) odds reduction; 2P=0·002) among patients who had undergone a vascular procedure as among other types of patient.

Treatment for only six months of 1000 patients who have had coronary revascularisation procedures might therefore not only prevent several dozen from having coronary artery occlusions but, even more important, might avoid a few dozen serious or fatal clinical vascular events.[5] Even among patients with peripheral arterial disease alone (who are at lower risk of myocardial infarction, stroke, or vascular death) treatment of 1000 patients with a year or two of antiplatelet therapy might not only prevent several dozen from having peripheral artery occlusions but also avert several more serious vascular events.[5]

Among haemodialysis patients antiplatelet therapy reduced the risk of occlusion of fistulas and shunts by about two thirds. The monthly rate of occlusion was high in these studies, and antiplatelet therapy reduced it from about 20% per month to about 10% per month (2P<0·00001; fig 2). It is relevant that these patients also suffer a particularly high incidence of serious vascular events[6] that could be reduced by prolonged antiplatelet treatment.

RISK OF BLEEDING

Many patients at very high risk of subclinical occlusion or vascular events (for example, those with unstable angina or with suspected acute myocardial infarction who are having emergency coronary artery bypass surgery or angiography) have been denied antiplatelet therapy for fear of perioperative bleeding.[89,90] This overview of trials of antiplatelet therapy during and after surgery suggests that the substantial benefits of such therapy (fig 2) generally outweigh any risks of bleeding (table). Detailed analysis of bleeding complications in a trial of aspirin started preoperatively in patients having coronary artery bypass surgery found a small but significant increase in drainage from the chest tube, in perioperative transfusion requirements, and in the reoperation rate, but there was no excess mortality due to bleeding complications.[30]

It has been suggested that starting antiplatelet therapy after invasive vascular procedures may reduce the risk of bleeding while still preventing occlusion.[11] No direct randomised comparisons of starting before or just after vascular procedures were available for this overview, but indirect comparisons suggested that similar reductions in occlusion were produced by starting treatment before and just after these procedures. More recently, the results of a trial have been reported among 351 patients randomly allocated to receive aspirin starting preoperatively or six hours after coronary artery bypass graft surgery.[91] Aspirin (325 mg daily) started preoperatively was associated with more blood being transfused (900 ml *v* 725 ml; 2P<0·05) and with more reoperations for bleeding (6·3% *v* 2·4%; 2P=0·07). But there were no statistically significant differences between the treatment groups in graft occlusion at an average of eight days after surgery (30 of 176 patients allocated preoperative antiplatelet therapy versus 27 of 175 allocated postoperative therapy), reinforcing—if on smaller numbers—the conclusion suggested by figure 3 that treatment started just after the vascular procedure may be about as effective as treatment started preoperatively.

CHOICE OF ANTIPLATELET REGIMEN

Comparisons between different antiplatelet regimens may be based on several factors, including efficacy, ease of use, severity of side effects, and cost. This overview provides some direct and indirect randomised comparisons of the effects of different drug regimens on the prevention of occlusion but finds no evidence of any differences in efficacy. The numbers of patients studied and the numbers of events that occurred were, however, not large enough (even with the inclusion of recent trials[92-94]; appendices 1 and 2) to exclude some small but real differences in efficacy between different drug regimens. Consequently, the choice of which regimen to use must be determined by other factors. At present medium dose aspirin is the most widely tested, most convenient, and least expensive antiplatelet treatment, with direct evidence of substantial reductions in occlusion and in important vascular events[5] that would generally far outweigh any small risks of bleeding. The choice of which antiplatelet regimen to use is, however, of secondary importance: what chiefly matters is that some such treatment should routinely be considered for the vast majority of patients having vascular procedures.

DURATION OF ANTIPLATELET TREATMENT

It remains uncertain how long antiplatelet therapy should be continued after vascular procedures. As yet there are no large directly randomised comparisons of different durations of treatment (though a recent small trial comparing two weeks versus six months of aspirin after coronary angioplasty suggested some additional effect on restenosis with continued treatment[95]). The highest absolute risk of occlusion generally occurs during the first few months, while any traumatic damage is healing, but even after those first few months a small percentage of patients per year may suffer late occlusions, as well as other more serious vascular events. The average duration of treatment in these trials was only about one year, but indirect evidence from studies in other settings suggests that more prolonged treatment may be more effective (see part I). It may therefore be prudent to consider continuing antiplatelet therapy after vascular procedures for as long as the risk of occlusive vascular events remains high.

Clinical implications

- Patients who have undergone coronary artery bypass grafting or angioplasty or leg artery bypass grafting or angioplasty are at high risk of both major clinical "vascular events" (myocardial infarction, stroke, or vascular death) and subclinical vascular occlusions
- As well as preventing about one quarter of clinical vascular events in patients undergoing such vascular procedures, antiplatelet therapy also reduced the odds of vascular graft or arterial occlusion by about 40% while treatment continued
- Typically, among 1000 patients who have coronary artery revascularisation procedures, about six months of antiplatelet therapy should prevent several dozen patients from having coronary artery occlusion as well as a few dozen major clinical vascular events
- Patients who have peripheral artery revascularisation procedures tend to be at lower risk of vascular events, but even so about one or two years of antiplatelet therapy in 1000 such patients should not only prevent several dozen from having peripheral artery occlusion but also avoid several major vascular events
- Antiplatelet therapy also substantially reduced the rate of occlusion of arteriovenous fistulas or shunts established for haemodialysis access (and should also reduce the high incidence of major vascular events in such patients)

Appendix 1

INDIVIDUAL RESULTS OF UNCONFOUNDED RANDOMISED COMPARISONS OF ANTIPLATELET THERAPY WITH CONTROL (AvC) FOR MAINTAINING VASCULAR PATENCY

Trial name†	Reference No	Regimen‡	Control and follow up methods§	Months of treatment	No of patients randomised		No with follow up¶		Vascular occlusion		Reoperation, wound haematoma/infection		Major bleed		Fatal bleed	
					A	C‖	A	C	A	C	A	C	A	C	A	C
Post-coronary artery bypass grafting																
McEnany	14	A1200	P A	18	71	77	40	37	15	16	—	—	0	0	0	0
Brooks	15, 16	A990+Dip	P A	12	160	160	133	133	33	37	—	—	3	1	1	0
Mayo-A	17-19	A925+Dip	P A	12	202	205	171	172	37	81	9	8	0	1	0	0
Liège-I	20-22	Ticlopidine	P A+S	3	75	75	42	35	7	11	1	10	0	0	0	0
Liège-II	23, 24	Ticlopidine	P A	12	88	87	79	75	30	39	—	—	0	0	0	0
Pantely	25	A975+Dip	O A	6	18	30	13	24	4	9	0	0	0	0	0	0
Wadsworth	26	A975,A+Dip	P A	12	96	51×2	83	44	25	18	—	—	—	—	0	0
Lorenz	27, 28	A100	P A	4	29	31	22	24	6	15	—	—	0	0	0	0
VA cooperative CABG	29. 30	A975,Sp,A+Dip	P A	12	619	153×4	395	107	138	47	33	2	30	2	0	0
GESIC	31	A150,A+Dip	P A	<1	741	371×2	612	315	168	114	26	16	16	5	0	0
Basle	32	A50+Dip	P A	9	62	63	58	57	17	20	1	2	0	0	0	0
Leeds-B	33	A990+Dip	P A	6	61	64	35	46	8	24	4	4	1	1	0	0
Czech	34	A1000+Dip	O A	12	47	46	25	29	13	27	—	—	0	0	0	0
Thaulow	35	A1000+Dip	P A	3	34	35	29	33	21	14	3	3	2	0	0	0
Guiteras	36	A150+Dip	P A	7	72	68	57	51	11	15	—	—	0	0	2	0
Sydney	37	A324	P A	12	68	69	56	49	7	17	—	—	1	0	—	—
Zurich	38	Ticlopidine	P A	3	50	50	42	45	9	8	12	2	12	2	0	0
Knudsen-B	39	Ticlopidine	P A	6	9	10	9	10	3	4	1	0	1	0	—	—
Romeo	40	Ticlopidine	O A	3	20	20	20	20	0	2	—	—	—	—	0	0
Baur	41	Sp	P A	<1	130	125	89	93	8	19	—	—	0	0	0	0
[EPPAC]	93	Dip	P A	6	—	—	182	196	35	32	—	—	—	—	—	—
[Ekeström]	94	Dip	P A	12	174	186	126	129	58	68	—	—	—	—	—	—
Post-percutaneous transluminal coronary angioplasty																
TACT	44	Ticlopidine	P A	6	177	173	121	123	6	17	—	—	0	0	1	0
Toronto	45	A990+Dip	P A	6	187	189	187	189	6	13	—	—	0	0	0	0
Finci	46	Suloctidil	P A	6	54	53	(54	53)	5	3	—	—	0	0	0	0
Intermittent claudication																
Schoop-I	47-49	A990, A+Dip	P A	60	200	100×2	(200	100)	39	39	—	—	3	0	0	0
Non-coronary artery grafting																
Rochester	51	A975,A+Dip	P C+A	12	32	17×2	(32	17)	8	12	—	—	2	0	0	0
McCollum	52	A600+Dip	P D+S	30	286	263	(286	263)	86	86	—	—	3	3	1	0
Kester	53.54	A990+Dip	P D+S	12	33	32	(33	32)	4	15	—	—	0	0	0	0
Kohler	55	A975+Dip	P D/P+A	24	50	50	44	44	15	12	—	—	—	—	0	0
Loew bypass	56,57	A1500	P C+A	12	215	213	139	141	24	47	—	—	1	2	0	0
Schettler	58	Sp	P D/P+A	6	33	30	27	27	4	4	—	—	0	0	0	0
Blakely-PVD	59	Sp	P C+A	36	75	90	75	89	11	11	—	—	0	0	0	0
Basellini	60	Ticlopidine	P D	6	25	25	23	23	3	6	0	1	0	1	0	0
Goldman	61,62	A900+Dip	P D+S	12	22	31	21	28	7	19	—	—	—	—	0	0
Zekert-IV	63	A1500	P C	<1	148	150	148	150	19	28	15	10	0	1	1	1
Harjola graft	64	A1500,Dip,A+Dip	O C+A	<1	300	100×3	278	86	12	12	0	0	—	—	—	—
Peripheral angioplasty																
Heiss	66,67	A300+Dip,A990+Dip	P A	6	132	67×2	98	47	15	13	—	—	0	0	0	0
Bern/Zurich	68	Suloctidil	P D	12	62	61	48	51	6	10	—	—	1	0	0	0
Haemodialysis access																
Pineo	70-72	Sp	P C	6	30	32	24	28	12	24	—	—	2	1	0	0
Majerus	73	A160	P C	5	19	25	(19	25)	6	18	—	—	0	0	0	0
Andrassy	74	A500	P C	1	47	45	(47	45)	2	11	2	2	2	2	0	0
Portsmouth-A	75	Ticlopidine	P C	3	24	26	(24	26)	3	8	3	1	0	0	0	0
Edinburgh	76	Ticlopidine	P C	1	13	12	(13	12)	2	5	—	—	0	0	0	0
London-C	77	Ticlopidine	P C	1	8	10	8	10	1	5	—	—	0	0	0	0
Swedish	78	Ticlopidine	P C	1	21	21	21	21	3	8	—	—	0	0	0	0
Heidelberg-A	79	Ticlopidine	P C	1	36	33	(36	33)	4	1	—	—	0	1	0	0
Norfolk	80	Sp	P C	3	8	8	8	8	1	2	—	—	0	0	0	0

—Data not available.
†Trials named within square brackets [] were major trials for which results became available after March 1990 deadline for overview.
‡A=Aspirin (expressed with daily dosage in mg, unless same in both arms). Dip=Dipyridamole. Sp=Sulphinpyrazone.
§P=Placebo. O=Open randomised control. A=Angiography. S=Radionuclide scanning. C=Clinical examination. D=Doppler ultrasonography. P=Limb plethysmography. +="with confirmatory...."
‖"×2," "×3," "×4" denote control groups counted twice, thrice, four times in adjusted totals to balance larger treatment groups.
¶Figures within parentheses are numbers of patients originally randomised in trials that recorded occlusion but did not provide numbers having follow up assessment.

Appendix 2

INDIVIDUAL RESULTS OF UNCONFOUNDED RANDOMISED COMPARISONS OF ONE ANTIPLATELET REGIMEN WITH ANOTHER (A1 *v* A2) FOR MAINTAINING VASCULAR PATENCY

Trial name†	Reference No	Regimen‡	Control and follow up methods§	Months of treatment	No of patients randomised		No with follow up‖		Vascular occlusion		Reoperation, wound haematoma/infection		Major bleed		Fatal bleed	
					A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2
Post-coronary artery bypass grafting																
Sharma	42	A+Dip *v* A975	P A	12	60	64	48	50	20	22	—	—	—	—	0	0
Wadsworth	26	A+Dip *v* A975	P A	12	49	47	45	38	15	10	—	—	0	0	0	0
VA cooperative CABG	29,30	Sp *v* A325,A975	P A	12	148	309	96	200	34	69	3	24	5	19	0	0
VA cooperative CABG	29,30	A+Dip *v* A975	P A	12	162	155	99	96	35	37	6	10	6	7	0	0
VA cooperative CABG	29.30	A325 *v* A975	P A	12	154	155	104	96	32	37	14	10	12	7	0	0
VA cooperative CABG	29,30	A975+Dip *v* Sp	P A	12	162	148	99	96	35	34	6	3	6	5	0	0
GESIC	31	A+Dip *v* A150	P A	<1	368	373	309	303	83	85	14	12	8	8	0	0
SINBA	43	A975+Dip *v* Indobufen	P A	12	279	290	(279	290)	61	69	—	—	0	0	0	0
[CABADAS]	92	A+Dip *v* A50	P A	12	313	317	249	270	26	27	—	—	—	—	0	0
Intermittent claudication																
Schoop-I	47-49	A+Dip *v* A990	P A	60	100	100	(100	100)	23	16	—	—	3	0	0	0
Schoop-II	50	Ticlopidine *v* A1500	O C	24	31	31	(31	31)	5	4	—	—	0	0	0	0
Non-coronary artery grafting																
Rochester	51	A+Dip *v* A975	P C+A	12	16	16	(16	16)	6	2	—	—	1	1	0	0
Bollinger	65	A+Dip *v* A1000	P D/P+A	24	41	40	41	40	10	6	—	—	0	0	0	0
Harjola graft	64	A1500+Dip *v* Dip	O C+A	<1	100	100	93	93	0	6	0	0	—	—	—	—
Harjola graft	64	A+Dip *v* A1500	O C+A	<1	100	100	93	92	0	6	0	0	—	—	—	—
Harjola graft	64	Dip *v* A1500	O C+A	<1	100	100	93	92	6	6	0	0	—	—	—	—
Peripheral angioplasty																
Heiss	66,67	A300+Dip *v* A990+Dip	P A	6	66	66	47	51	4	11	—	—	0	0	0	0
Hess-PTA	69	A+Dip *v* A990	P —	<1	55	55	(55	55)	8	15	—	—	0	0	0	0
Haemodialysis access																
Albert	81	Sp *v* A1500	O C	1	19	17	(19	17)	0	1	—	—	0	2	0	0
Heidelberg-B	82	Ticlopidine *v* A500	P —	1	10	10	(10	10)	2	2	—	—	—	—	—	—

—Data not available.
†Trials named within square brackets [] were major trials for which results became available after March 1990 deadline for overview.
‡A=Aspirin (expressed with daily dosage in mg, unless same in both arms). Dip=Dipyridamole. Sp=Sulphinpyrazone.
§P=Placebo. O=Open randomised control. A=Angiography. C=Clinical examination. D=Doppler ultrasonography. P=Limb plethysmography. +="with confirmatory..."
‖Figures within parentheses are numbers of patients originally randomised in trials that recorded occlusion but did not provide numbers having follow up assessment.

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Management of breast cancer in southeast England

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Abstract

***Objective*—To examine the extent to which management of invasive breast cancer reflected consensus guidelines in the Thames regions in 1990.**

***Design*—Population based study of case notes.**

***Setting*—Thames Cancer Registry.**

***Subjects*—All women with breast cancer diagnosed in early 1990 (417 cases) resident in the four Thames regions. Hospital records were traced for 346 cases, of which 12 were ineligible because of misclassification in initial registration and were excluded from the analysis. 334 cases were analysed.**

***Main outcome measures*—Investigations and treatment in the six months after diagnosis, stage of disease.**

***Results*—Of the 334 women identified, 86 were aged under 50. Three years after diagnosis, 74 were dead, seven (8%) aged under 50 and 67 (27%) aged 50 or over. Axillary surgery was used to stage cancer in only 155 cases (46%), although this is recommended in the guidelines. Only 79 (24%) case notes had any information recorded on stage. Stage could be determined reliably for only half of the sample. Treatment varied widely within the same age group and stage of disease. In particular, chemotherapy was not routinely given to patients under 50 with stage II disease. Only 17 records showed evidence that the patient was participating in a clinical trial.**

***Conclusions*—There was a lack of consensus on the management of breast cancer among clinicians in 1990. More patients should be included in clinical trials.**

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Introduction

Wide variations in the management of breast cancer patients in London hospitals were found by two studies during 1982-6.[1,2] In 1986, the King's Fund consensus conference published guidelines for treatment of breast cancer, providing a standard against which care can be audited.[3] The guidelines recommended that axillary lymph nodes should be sampled at surgery to enable staging of disease and that combination chemotherapy should be used to reduce the risk of death in women younger than 50, particularly in those with lymph node disease at diagnosis. Tamoxifen was recommended to reduce mortality in women aged over 50. Additional evidence of the value of tamoxifen and chemotherapy has recently been found in the overview of trials of treatment of early breast cancer.[4]

We examined the extent to which the management of breast cancer in southeast England in 1990 reflected the consensus guidelines. Monitoring the management of breast cancer is important, both for the evaluation of the national screening programme and for the British government's Health of the Nation target of reducing breast cancer mortality by 25% in women aged 50-65 by the year 2000.[5-7]

Methods

We studied the hospital records of 334 women who had invasive breast cancer diagnosed in early 1990 and who were registered in the Thames Cancer Registry, a population based registry covering about 14 million people living in the four Thames regional health authorities in southeast England.[8,9] Over 7500 cases of breast cancer in women are registered among this population every year. The annual incidence rates (world standardised) are 61 to 65 per 100 000. The five year relative survival for women aged 15-74 years diagnosed during 1980-4 was 63% to 67%.[8]

We included in the study all 249 primary malignant neoplasms of the breast (second contralateral breast cancers were excluded) diagnosed during 15-31 January 1990. These cases are being contributed to the Eurocare study of patterns of survival and cancer care across the European Community. In addition, North